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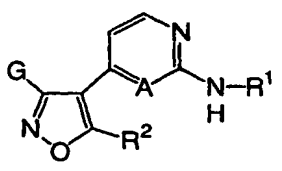
(54) Title: ISOXAXOLE DERIVATIVES AS INHIBITORS OF SRC AND OTHER PROTEIN KINASES



(I)

(57) Abstract: The present invention provides compounds of formula I: wherein A is N or CR, and R_1, G and R_2, are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of Src mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

ISOXAXOLE DERIVATIVES AS INHIBITORS OF SRC AND OTHER PROTEIN KINASES

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to US Provisional Patent Application 60/282,935 filed April 10, 2001, the contents of which are incorporated herein by reference.

TECHNICAL FIELD OF INVENTION

The present invention relates to inhibitors of c-Jun N-terminal kinases (JNK) and kinases belonging to the Src family of protein kinases, especially Src and Lck protein kinases. Src kinases are implicated in cancer, immune disorders and bone diseases. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

BACKGROUND OF THE INVENTION

Mammalian cells respond to extracellular stimuli by activating signaling cascades that are mediated by members of the mitogen-activated protein (MAP) kinase family, which include the extracellular signal regulated kinases (ERKs), the p38 MAP kinases and the c-Jun N-terminal kinases (JNKs). MAP kinases (MAPKs) are activated by a variety of signals including growth factors, cytokines, UV radiation, and stress-inducing agents. MAPKs are serine/threonine kinases whose activation occurs by dual phosphorylation of threonine

and tyrosine at the Thr-X-Tyr segment in the activation loop. MAPKs phosphorylate various substrates including transcription factors, which in turn regulate the expression of specific sets of genes and thus mediate a specific response to the stimulus.

One kinase family of particular interest is the Src family of kinases. These kinases are implicated in cancer, immune system dysfunction and bone remodeling diseases. For general reviews, see Thomas and Brugge, *Annu. Rev. Cell Dev. Biol.* (1997) **13**, 513; Lawrence and Niu, *Pharmacol. Ther.* (1998) **77**, 81; Tatosyan and Mizenina, *Biochemistry* (Moscow) (2000) **65**, 49; Boschelli et al., *Drugs of the Future* 2000, **25**(7), 717, (2000).

Members of the Src family include the following eight kinases in mammals: Src, Fyn, Yes, Fgr, Lyn, Hck, Lck, and Blk. These are nonreceptor protein kinases that range in molecular mass from 52 to 62 kD. All are characterized by a common structural organization that is comprised of six distinct functional domains: Src homology domain 4 (SH4), a unique domain, SH3 domain, SH2 domain, a catalytic domain (SH1), and a C-terminal regulatory region. Tatosyan et al. *Biochemistry* (Moscow) **65**, 49-58 (2000).

Based on published studies, Src kinases are considered as potential therapeutic targets for various human diseases. Mice that are deficient in Src develop osteopetrosis, or bone build-up, because of depressed bone resorption by osteoclasts. This suggests that osteoporosis resulting from abnormally high bone resorption can be treated by inhibiting Src. Soriano et al., *Cell*, **69**, 551 (1992) and Soriano et al., *Cell*, **64**, 693 (1991).

Suppression of arthritic bone destruction has been achieved by the overexpression of CSK in rheumatoid synoviocytes and osteoclasts. Takayanagi et al., *J. Clin. Invest.*, **104**, 137 (1999). CSK, or C-terminal Src kinase, phosphorylates and thereby inhibits Src catalytic activity. This implies that Src inhibition may prevent joint destruction that is characteristic in patients suffering from rheumatoid arthritis. Boschelli et al., *Drugs of the Future* 2000, **25**(7), 717, (2000).

Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor HBx activates Src in a step required for propagation of the virus. Klein et al., *EMBO J.*, **18**, 5019, (1999) and Klein et al., *Mol. Cell. Biol.*, **17**, 6427 (1997).

A number of studies have linked Src expression to cancers such as colon, breast, hepatic and pancreatic cancer, certain B-cell leukemias and lymphomas. Talamonti et al., *J. Clin. Invest.*, **91**, 53 (1993); Lutz et al., *Biochem. Biophys. Res.*, **243**, 503 (1998); Rosen et al., *J. Biol. Chem.*, **261**, 13754 (1986); Bolen et al., *Proc. Natl. Acad. Sci. USA*, **84**, 2251 (1987); Masaki et al., *Hepatology*, **27**, 1257 (1998); Biscardi et al., *Adv. Cancer Res.*, **76**, 61 (1999); Lynch et al., *Leukemia*, **7**, 1416 (1993). Furthermore, antisense Src expressed in ovarian and colon tumor cells has been shown to inhibit tumor growth. Wiener et al., *Clin. Cancer Res.*, **5**, 2164 (1999); Staley et al., *Cell Growth Diff.*, **8**, 269 (1997).

Other Src family kinases are also potential therapeutic targets. Lck plays a role in T-cell signaling. Mice that lack the Lck gene have a poor ability to develop thymocytes. The function of Lck as a positive activator of T-cell signaling suggests that Lck

inhibitors may be useful for treating autoimmune disease such as rheumatoid arthritis. Molina et al., *Nature*, **357**, 161 (1992). Hck, Fgr and Lyn have been identified as important mediators of integrin signaling in myeloid leukocytes. Lowell et al., *J. Leukoc. Biol.*, **65**, 313 (1999). Inhibition of these kinase mediators may therefore be useful for treating inflammation. Boschelli et al., *Drugs of the Future* 2000, **25**(7), 717, (2000).

In the c-Jun NH_2-terminal protein kinases, also known as JNKs, three distinct genes, JNK1, JNK2, JNK3 have been identified and at least ten different splicing isoforms of JNKs exist in mammalian cells [Gupta et al., *EMBO J.*, **15**, 2760-70 (1996)]. Members of the JNK family are activated by proinflammatory cytokines, such as tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β), as well as by environmental stress, including anisomycin, UV irradiation, hypoxia, and osmotic shock [Minden et al., *Biochemica et Biophysica Acta*, **1333**, F85-F104 (1997)].

The down-stream substrates of JNKs include transcription factors c-Jun, ATF-2, Elk1, p53 and a cell death domain protein (DENN) [Zhang et al., *Proc. Natl. Acad. Sci. USA*, **95**, 2586-91 (1998)]. Each JNK isoform binds to these substrates with different affinities, suggesting a regulation of signaling pathways by substrate specificity of different JNKs *in vivo* (Gupta et al., *supra*).

JNKs, along with other MAPKs, have been implicated in the mediation of cellular response to cancer, thrombin-induced platelet aggregation, immunodeficiency disorders, autoimmune diseases, cell death, allergies, osteoporosis and heart disease. The therapeutic conditions related to activation of the JNK pathway include chronic myelogenous leukemia (CML),

rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer and neurodegenerative diseases.

Several reports have detailed the importance of JNK activation associated with liver disease or episodes of hepatic ischemia [*Nat. Genet.* **21**, 326-9 (1999); *FEBS Lett.* **420**, 201-4 (1997); *J. Clin. Invest.* **102**, 1942-50 (1998); *Hepatology* **28**, 1022-30 (1998)].

A role for JNK in cardiovascular disease such as myocardial infarction or congestive heart failure has also been reported as it has been shown JNK mediates hypertrophic responses to various forms of cardiac stress [*Circ. Res.* **83**, 167-78 (1998); *Circulation* **97**, 1731-7 (1998); *J. Biol. Chem.* **272**, 28050-6 (1997); *Circ. Res.* **79**, 162-73 (1996); *Circ. Res.* **78**, 947-53 (1996); *J. Clin. Invest.* **97**, 508-14 (1996)].

It has been demonstrated that the JNK cascade also plays a role in T-cell activation, including activation of the IL-2 promoter. Thus, inhibitors of JNK have potential therapeutic value in altering pathologic immune responses [*J. Immunol.* **162**, 3176-87 (1999); *Eur. J. Immunol.* **28**, 3867-77 (1998); *J. Exp. Med.* **186**, 941-53 (1997); *Eur. J. Immunol.* **26**, 989-94 (1996)].

A role for JNK activation in various cancers has also been established, suggesting the potential use of JNK inhibitors in cancer. For example, constitutively activated JNK is associated with HTLV-1 mediated tumorigenesis [*Oncogene* **13**, 135-42 (1996)]. The proliferative effects of bFGF and OSM on Kaposi's sarcoma (KS) cells are mediated by their activation of the JNK signaling pathway [*J. Clin. Invest.* **99**, 1798-804 (1997)]. Other proliferative effects of other cytokines implicated in KS proliferation, such as vascular endothelial growth factor (VEGF), IL-6 and TNFα, are also mediated by JNK.

In addition, regulation of the c-jun gene in p210 BCR-ABL transformed cells corresponds with activity of JNK, suggesting a role for JNK inhibitors in the treatment for chronic myelogenous leukemia (CML) [*Blood* **92**, 2450-60 (1998)].

JNK1 and JNK2 are widely expressed in a variety of tissues. In contrast, JNK3 is selectively expressed in the brain and to a lesser extent in the heart and testis [Gupta et al., *supra*; Mohit et al., *Neuron* **14**, 67-78 (1995); Martin et al., *Brain Res. Mol. Brain Res.* **35**, 47-57 (1996)]. JNK3 has been linked to neuronal apoptosis induced by kainic acid, indicating a role of JNK in the pathogenesis of glutamate neurotoxicity. In the adult human brain, JNK3 expression is localized to a subpopulation of pyramidal neurons in the CA1, CA4 and subiculum regions of the hippocampus and layers 3 and 5 of the neocortex [Mohit et al., *supra*]. The CA1 neurons of patients with acute hypoxia showed strong nuclear JNK3-immunoreactivity compared to minimal, diffuse cytoplasmic staining of the hippocampal neurons from brain tissues of normal patients [Zhang et al., *supra*]. Thus, JNK3 appears to be involved involved in hypoxic and ischemic damage of CA1 neurons in the hippocampus.

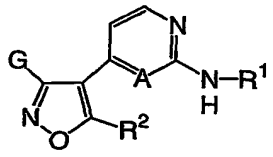
In addition, JNK3 co-localizes immunochemically with neurons vulnerable in Alzheimer's disease [Mohit et al., *supra*]. Disruption of the JNK3 gene caused resistance of mice to the excitotoxic glutamate receptor agonist kainic acid, including the effects on seizure activity, AP-1 transcriptional activity and apoptosis of hippocampal neurons, indicating that the JNK3 signaling pathway is a critical component in the pathogenesis of glutamate neurotoxicity (Yang et al., *Nature*, **389**, 865-870 (1997)].

Based on these findings, JNK signaling, especially that of JNK3, has been implicated in the areas of apoptosis-driven neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, ALS (Amyotrophic Lateral Sclerosis), epilepsy and seizures, Huntington's Disease, traumatic brain injuries, as well as ischemic and hemorrhaging stroke.

Accordingly, there is still a great need to develop potent inhibitors of JNK3, Src, and Lck protein kinases that are useful in treating various diseases or conditions associated with JNK3, Src, and Lck activation.

SUMMARY OF THE INVENTION

It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of Src, Lck, and JNK3 protein kinases. These compounds have the general formula I:



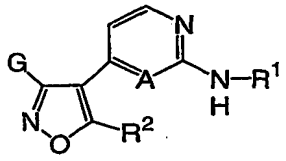
I

or a pharmaceutically acceptable derivative thereof, wherein A is nitrogen or CH, and R^1, R^2, and G are as described below.

These compounds, and pharmaceutically acceptable compositions comprising them, are useful for treating or reducing the risk of a variety of disorders, such as cancer, autoimmune disease, osteoporosis, and inflammatory diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of formula I:



I

or a pharmaceutically acceptable derivative thereof, wherein:

G is -XR or -XAr;

each X is independently selected from a C_{1-6} alkylidene chain wherein one or two non-adjacent methylene units of X are optionally and indpendently replaced by -O-, -NR-, -S-, -C(O)-, -C(O)NR-, -NRC(O)-, -NRC(O)NR-, -SO-, $-SO_2-$, $-NRSO_2-$, $-SO_2NR-$, or $-NRSO_2NR-$;

A is N or CR;

each R is independently selected from hydrogen or an optionally substituted C_{1-8} aliphatic group, or

two R groups bound to the same nitrogen are taken together with the nitrogen to form a 3-7 membered heterocyclic ring having 0-2 heteroatoms in addition to the nitrogen, and independently selected from nitrogen, oxygen, or sulfur; provided that when G is $-N(R)_2$, the two R groups are not taken together to form a ring;

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or aryl monocyclic ring having zero to three heteroatoms independently selected from nitrogen, sulfur, or oxygen, or an optionally substituted 8-10 membered saturated, partially unsaturated, or aryl bicyclic ring having zero to four heteroatoms independently selected from nitrogen, sulfur, or oxygen;

R^1 is $T_{(n)}$-R or $T_{(n)}$-Ar;

n is zero or one;

T is selected from -C(O)-, $-CO_2-$, -C(O)C(O)-, $-C(O)CH_2C(O)-$, -CONR-, $-S(O)_2-$, or $-S(O)_2NR-$; and

each R^2 is independently selected from -R, $-CH_2OR$, -CH(O), $-CH_2SR$, $-CH_2S(O)_2R$, $-CH_2C(O)R$, $-CH_2CO_2R$, $-CH_2CN$, $-CH_2N(R)_2$, -CH=N-OR, $-CH=NN(R)_2$, -CH=NNHCOR, $-CH=NNHCO_2R$, $-CH=NNHSO_2R$, Ar, $-CH_2Ar$, $-CH_2NRCON(R)_2$, $-CH_2NRCOR$, $-CH_2NRCO_2R$, $-CH_2CON(R)_2$, $-CH_2SO_2N(R)_2$, or $-CH_2NRSO_2N(R)_2$.

As used herein, the following definitions shall apply unless otherwise indicated.

The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "aliphatic" or "aliphatic group" as used herein means a straight-chain or branched C_1-C_8 hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched or alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety include both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, $-R^\circ$, $-OR^\circ$, $-SR^\circ$, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph) optionally substituted with R°, $-O(Ph)$ optionally substituted with R°, $-CH_2(Ph)$ optionally substituted with R°, $-CH_2CH_2(Ph)$, optionally substituted with R°, $-NO_2$, $-CN$, $-N(R^\circ)_2$, $-NR^\circC(O)R^\circ$, $-NR^\circC(O)N(R^\circ)_2$, $-NR^\circCO_2R^\circ$, $-NR^\circNR^\circC(O)R^\circ$, $-NR^\circNR^\circC(O)N(R^\circ)_2$, $-NR^\circNR^\circCO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R^\circ)_2$, $-S(O)R^\circ$, $-NR^\circSO_2N(R^\circ)_2$, $-NR^\circSO_2R^\circ$, $-C(=S)N(R^\circ)_2$, $-C(=NH)-N(R^\circ)_2$, or $-(CH_2)_yNHC(O)R^\circ$, wherein each R° is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, $-O(Ph)$, or $-CH_2(Ph)$. Optional substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH,

O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic.

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following: =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R* are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic).

Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-CH_2CH_2$(Ph), or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic).

The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully

saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

Preferred G groups of formula I are -X-R and -X-Ar, wherein X is a C_{1-4} alkylidene chain and wherein one or two non-adjacent methylene units of X are independently replaced by -S-, -SO-, -SO_2-, -O-, or -NH-. More preferred X groups of formula I are selected from

-S-, -O-, -NH-, $-SO_2-$, $-NHCH_2CH_2NHCH_2CH_2-$, $-NHCH_2CH_2CH_2-$, $-NHCH_2CH_2OCH_2CH_2-$, or $-NHCH_2CH_2-$.

Preferred R groups within the -X-R moiety of formula **I** are selected from an optionally substituted C_{1-6} aliphatic group and more preferably an optionally substituted C_{1-4} alkyl. Preferred substituents on the R group of -X-R of formula **I** are selected from halo, CN, oxo, $N(R^\circ)_2$, OH, OR°, CO_2R°, $C(O)R^\circ$, $C(O)N(R^\circ)_2$, $NR^\circ CO_2R^\circ$, SR°, $NR^\circ SO_2R^\circ$, SO_2R°, $NR^\circ C(O)R^\circ$, $OC(O)R^\circ$, or $NR^\circ C(O)N(R^\circ)_2$, wherein each R° group is independently selected from hydrogen or C_{1-4} aliphatic. Most preferred R groups of -X-R of formula **I** are selected from methyl, ethyl, isopropyl, isobutyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, CH_2CN, CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2CF_3$, CH_2cyclopropyl, $CH_2C(O)CH_3$, $CH_2CH_2N(Me)_2$, $CH_2CH_2NHC(O)CH_3$, $CH_2CH_2NHCO_2CH_3$, $CH_2CH_2OC(O)CH_3$, $CH_2CH(NH_2)CO_2Et$, $CH_2C{\equiv}CCH_3$, or $CH_2CH(Me)_2$.

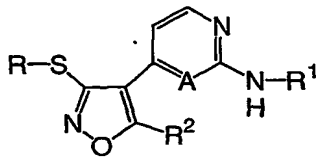
Preferred Ar groups within the -X-Ar moiety of formula **I** are selected from an optionally substituted 5-6 membered saturated or aryl ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered bicyclic aryl or heteroaryl ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred Ar groups within -X-Ar of formula **I** are optionally substituted rings selected from phenyl, pyridyl, imidazolyl, thienyl, thiazolyl, [1,3]dioxanyl, piperidinyl, morpholinyl, pyrrolyl, pyrrolidinyl, furanyl, tetrahydrofuranyl, pyranyl, imidazolyl, benzimidazolyl, pyrrolyl, piperazinyl, thiomorpholinyl, naphthyl, oxazolyl, triazinyl, tetrazolyl, dithiolanyl, dioxalanyl, benzofuranyl, benzothienyl, or indolyl.

Preferred R^1 groups of formula I are $T_{(n)}$-Ar wherein n is zero. Preferred Ar groups within the R^1 moiety are selected from an optionally substituted 6-membered saturated or aryl ring having 0-2 nitrogens, or an optionally substituted 9-10 membered partially unsaturated or fully unsaturated bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred Ar groups within the R^1 moiety are optionally substituted rings selected from phenyl, cyclohexyl, pyridyl, naphthyl, quinolinyl, isoquinolinyl, or indanyl.

Preferred substituents on Ar of R^1 of formula I are selected from R°, halogen, NO_2, CN, OR°, SR°, $N(R^\circ)_2$, CO_2R°, $C(O)R^\circ$, $CON(R^\circ)_2$, phenyl, SO_2R°, or $NR^\circ C(O)R^\circ$, wherein each R° is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic. More preferred substituents on Ar of R^1 of formula I are selected from methyl, ethyl, oxo, CF_3, OMe, C(O)Me, C(O)phenyl, CH≡CH, CO_2H, $C(O)NH_2$, SMe, CO_2Me, fluoro, SO_2Me, NO_2, CN, chloro, $N(Me)_2$, NHC(O)Me, NH_2, cyanophenyl, CO_2Et, CH_2OH, CH_2OMe, 3-CH_2CO_2H-phenyl, or 3-$CH_2CH_2CO_2H$-phenyl.

Preferred R^2 groups of formula I are selected from R, $CH_2N(R)_2$, or CH_2Ar, wherein R is hydrogen or optionally substituted C_{1-4} aliphatic, and Ar is an optionally substituted 6 membered saturated or unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred R^2 groups of formula I are methyl, ethyl, CH_2(morpholin-4-yl), $CH_2N(Me)_2$, $CH_2N(Et)_2$, $CH_2N(Me)CH_2CO_2CH_3$, or CH_2(piperazin-1-yl).

A preferred embodiment of this invention relates to a compound of formula I where G is S-R, as shown by the general formula IA below:

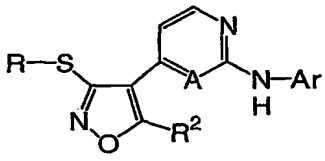


IA

or a pharmaceutically acceptable derivative thereof, wherein A, R, R^1 and R^2 are as defined above.

Preferred R, R^1, and R^2 groups of formula **IA** are those described for formula **I** above.

According to a more preferred embodiment, the present invention relates to a compound of formula **IIA**:



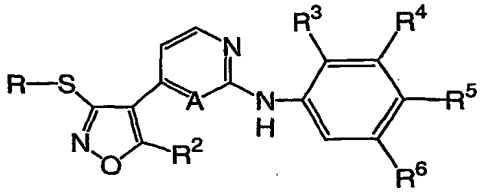
IIA

or a pharmaceutically acceptable derivative thereof, wherein A, R, Ar, and R^2 are as defined above.

Preferred Ar, R, and R^2 groups of formula **IIA** are those described for formula **I** above.

Table 1 below shows representative examples of **IIA** compounds wherein Ar is an optionally substituted phenyl ring.

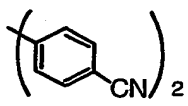
Table 1. Examples of Compounds of Formula **IIA**:

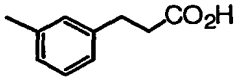
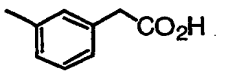
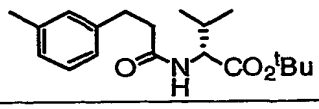


No.	S-R	A	R^2	R^3	R^4	R^5	R^6
IIA-1	SCH_3	N	Me	H	H	H	H
IIA-2	SCH_3	N	Me	H	H	OMe	H
IIA-3	SCH_3	N	Me	H	OMe	OMe	H

No.	S-R	A	R^2	R^3	R^4	R^5	R^6
IIA-4	SCH_3	N	Me	Me	H	H	H
IIA-5	SCH_3	N	Me	Me	H	$CONH_2$	H
IIA-6	SCH_3	N	Me	Me	H	CN	H
IIA-7	SCH_3	N	Me	H	CN	H	H
IIA-8	SCH_3	N	Me	Me	F	H	H
IIA-9	SCH_3	N	Me	Me	H	F	H
IIA-10	SCH_3	N	Me	CF_3	H	H	H
IIA-11	SCH_3	CH	Et	H	CN	H	H
IIA-12	SCH_3	CH	Et	H	CO_2H	H	H
IIA-13	SCH_3	CH	Me	H	F	H	H
IIA-14	SCH_3	CH	Me	H	H	F	H
IIA-15	SCH_3	CH	Me	H	H	COMe	H
IIA-16	SCH_3	CH	Me	H	H	COPh	H
IIA-17	SCH_3	CH	Me	H	H	$CONH_2$	H
IIA-18	SCH_3	N	Me	H	OMe	H	OMe
IIA-19	SCH_3	N	Me	H	F	H	H
IIA-20	SCH_3	N	Me	H	H	CN	H
IIA-21	SCH_3	N	Me	H	H	COMe	H
IIA-22	SCH_3	N	Me	H	CH=CH	H	H
IIA-23	SCH_3	N	Me	H	SMe	H	H
IIA-24	SCH_3	N	Me	H	Me	CN	H
IIA-25	SCH_3	N	Me	H	COMe	H	H
IIA-26	SCH_3	CH	Et	H	H	H	H
IIA-27	SCH_3	N	Me	OMe	H	H	H
IIA-28	SCH_3	N	Me	H	H	F	H
IIA-29	SCH_3	CH	Me	H	CO_2H	H	H
IIA-30	SCH_3	N	Me	H	H	Ph	H
IIA-31	SCH_3	N	Me	H	Me	H	Me
IIA-32	SCH_3	N	Me	H	H	SMe	H
IIA-33	SCH_3	CH	Me	H	H	OMe	H
IIA-34	SCH_3	CH	Me	H	OMe	H	H
IIA-35	SCH_3	N	Me	OMe	H	H	CN
IIA-36	SCH_3	CH	Me	H	CO_2Me	H	H
IIA-37	SCH_3	N	Me	F	H	H	CN
IIA-38	SCH_3	CH	Me	H	H	H	H
IIA-39	SCH_3	CH	Me	H	H	CO_2H	H

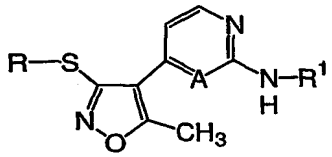
No.	S-R	A	R^2	R^3	R^4	R^5	R^6
IIA-40	SCH_3	N	Me	Me	H	CN	H
IIA-41	SCH_3	N	Me	F	H	F	H
IIA-42	SCH_3	N	Me	Me	H	$CONH_2$	H
IIA-43	SCH_3	N	Me	Me	Cl	H	H
IIA-44	SCH_3	N	Me	F	H	H	H
IIA-45	SCH_3	N	Me	Me	H	OMe	H
IIA-46	SCH_3	N	Me	OMe	H	H	H
IIA-47	SCH_3	N	Me	H	H	SO_2Me	H
IIA-48	SCH_3	CH	Me	H	H	CO_2Me	H
IIA-49	SCH_3	N	Me	NO_2	H	H	H
IIA-50	SCH_3	CH	Me	H	CN	H	H
IIA-51	SCH_3	CH	Me	H	H	CN	H
IIA-52	SCH_3	N	Me	$CHCH_2$	H	H	H
IIA-53	SCH_3	N	Me	Me	F	H	H
IIA-54	SCH_3	N	Me	Cl	H	H	OMe
IIA-55	SCH_3	N	Me	H	Me	OMe	H
IIA-56	SCH_3	N	Me	Me	H	F	H
IIA-57	SCH_3	N	Me	SMe	H	H	H
IIA-58	SCH_3	N	Me	OMe	H	H	OMe
IIA-59	SCH_2CH_3	N	Me	H	H	H	H
IIA-60	SCH_2CH_3	N	Me	H	CN	H	H
IIA-61	SCH_2CH_3	N	Me	H	H	CN	H
IIA-62	SCH_2CH_3	N	Me	H	F	H	H
IIA-63	SCH_2CH_3	N	Me	H	H	F	H
IIA-64	SCH_2CH_3	N	Me	H	Me	CN	H
IIA-65	SCH_2CH_3	N	Me	H	F	CN	H
IIA-66	SCH_2CH_3	N	Me	H	H	SMe	H
IIA-67	$SCH(CH_3)_2$	N	Me	H	H	H	H
IIA-68	$SCH_2CH(CH_3)_2$	N	Me	H	H	H	H
IIA-69	S-propyl	N	Me	H	H	H	H
IIA-70	S-butyl	N	Me	H	H	H	H
IIA-71	S-pentyl	N	Me	H	H	H	H
IIA-72	S-hexyl	N	Me	H	H	H	H
IIA-73	S-heptyl	N	Me	H	H	H	H
IIA-74	S-octyl	N	Me	H	H	H	H
IIA-75	SCH_2CN	N	Me	H	H	H	H

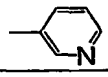
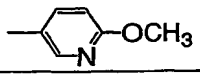
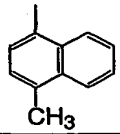
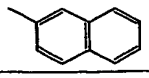
No.	S-R	A	R^2	R^3	R^4	R^5	R^6
IIA-76	$SCH_2CH_2OCH_3$	N	Me	H	H	H	H
IIA-77	$SCH_2CH_2CF_3$	N	Me	H	H	H	H
IIA-78	SCH_2(cyclopropyl)	N	Me	H	H	H	H
IIA-79	$SCH_2C(=O)CH_3$	N	Me	H	H	H	H
IIA-80	$SCH_2CH_2N(CH_3)_2$	N	Me	H	H	H	H
IIA-81	$SCH_2CH_2NHCOCH_3$	N	Me	H	H	H	H
IIA-82	$SCH_2CH_2NHCO_2CH_3$	N	Me	H	H	H	H
IIA-83	$SCH_2CH_2OC(=O)CH_3$	N	Me	H	H	H	H
IIA-84	$SCH_2CH(NH_2)CO_2Et$	N	Me	H	H	H	H
IIA-85	$SCH_2C\equiv CCH_3$	N	Me	H	H	H	H
IIA-86	S-propyl	N	Me	H	H	COMe	H
IIA-87	S-propyl	N	Me	H	CN	H	H
IIA-88	S-propyl	N	Me	H	H	CN	H
IIA-89	S-propyl	N	Me	H	F	H	H
IIA-90	S-propyl	N	Me	H	H	F	H
IIA-91	S-propyl	N	Me	H	CN	F	H
IIA-92	S-propyl	N	Me	H	H	SMe	H
IIA-93	SCH_3	CH	Me	H	H	NMe_2	H
IIA-94	SCH_3	CH	Me	H	NO_2	H	H
IIA-95	SCH_3	CH	Me	H	NHAc	H	H
IIA-96	SCH_3	CH	Me	H	NH_2	H	H
IIA-97	SCH_3	N	Me	H	Me	H	H
IIA-98	SCH_3	N	Me	H	H	Me	H
IIA-99	S-butyl	N	Me	H	F	CN	H
IIA-100	S-butyl	N	Me	H	F	H	H
IIA-101	S-butyl	N	Me	H	H	CN	H
IIA-102	S-butyl	N	Me	H	Me	H	H
IIA-103	S-butyl	N	Me	H	CN	H	H
IIA-105	S-pentyl	N	Me	H	F	CN	H
IIA-106	S-pentyl	N	Me	H	CN	H	H
IIA-107	$SCH_2CH(CH_3)_2$	N	Me	H	F	CN	H
IIA-108	$SCH_2CH(CH_3)_2$	N	Me	H	CN	H	H
IIA-109	$SCH_2CH(CH_3)_2$	N	Me	 bis-N,N'-4-cyanophenyl			

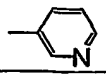
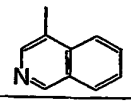
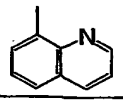
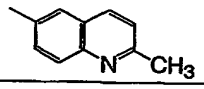
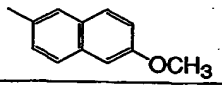
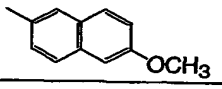
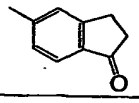
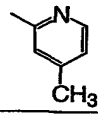
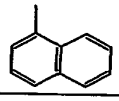
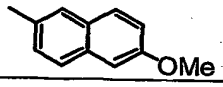
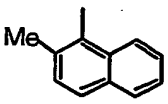
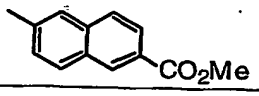
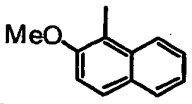
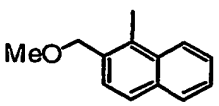
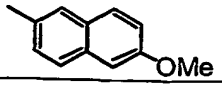
No.	S-R	A	R^2	R^3	R^4	R^5	R^6
IIA-110	$SCH_2C{\equiv}CCH_3$	N	Me	H	F	CN	H
IIA-111	$SCH_2C{\equiv}CCH_3$	N	Me	H	CN	H	H
IIA-112	$SCH_2C{\equiv}CCH_3$	N	Me	H	H	H	H
IIA-113	SCH_3	N	Me	H	CO_2Et	H	H
IIA-114	SCH_3	N	Me	N	H	NO_2	H
IIA-115	SCH_3	CH	Me				
IIA-116	SCH_3	CH	Me				
IIA-117	SCH_3	CH	Me	H	CH_2OH	H	H
IIA-118	SCH_3	CH	Me				

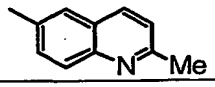
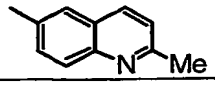
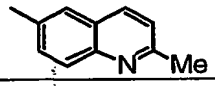
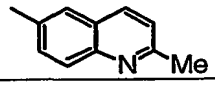
Examples of compounds of Formula **IIA** wherein R^2 is methyl and R^1 is other than phenyl are shown below in Table 2.

Table 2. Examples of Compounds of Formula **IIA**



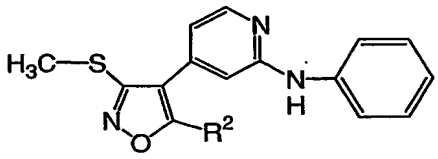
No.	S-R	A	R^1
IIA-119	SCH_3	CH	
IIA-120	SCH_3	CH	
IIA-121	SCH_3	N	
IIA-122	SCH_3	N	

No.	S-R	A	R^1
IIA-123	SCH_3	N	
IIA-124	SCH_3	N	
IIA-125	SCH_3	N	
IIA-126	SCH_3	N	
IIA-127	SCH_3	N	
IIA-128	SCH_3	N	
IIA-129	SCH_3	N	
IIA-130	SCH_3	N	
IIA-131	SCH_3	N	
IIA-132	S-propyl	N	
IIA-133	SCH_3	N	
IIA-134	SCH_3	N	
IIA-135	SCH_3	N	
IIA-136	SCH_3	N	
IIA-137	S-butyl	N	

No.	S-R	A	R^1
IIA-138	S-butyl	N	
IIA-139	S-CH_2CN	N	
IIA-140	S-CH_2CN	N	
IIA-141	S-CH_2CN	N	

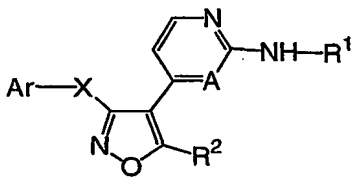
Representative examples of compounds of formula **IIA** wherein R^2 is other than methyl are shown in Table 3 below.

Table 3. Examples of Compound **IIA**

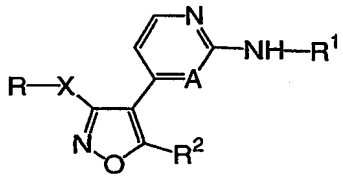


No.	R^2
IIA-142	CH_2(morpholin-4-yl)
IIA-143	$CH_2N(CH_3)_2$
IIA-144	CH_2NEt_2
IIA-145	$CH_2N(CH_3)CH_2Ph$
IIA-146	$CH_2N(CH_3)CH_2CO_2CH_3$
IIA-147	CH_2(piperazin-1-yl)

Another embodiment of this invention relates to a compound of formula **IB** or **IB'**:



IB



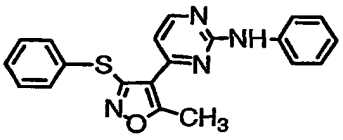
IB'

or a pharmaceutically acceptable derivative thereof, wherein X is independently selected from a C_{1-4} alkylidene chain and wherein one or two non-adjacent methylene units of X are optionally and independently replaced by -S-, -O-, or -NH-, and wherein A, R, Ar, R^1, and R^2 are as defined above.

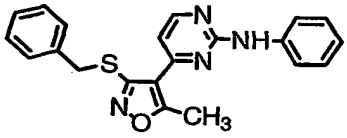
Preferred R, Ar, R^1 and R^2 groups within formulae **IB** and **IB'** are as described above for formula I.

Table 4 below shows specific examples of formula **IB** and **IB'** compounds.

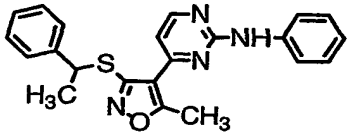
Table 4. Examples of **IB** Compounds



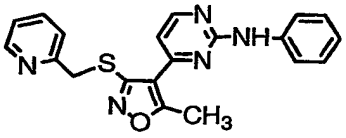
IB-1



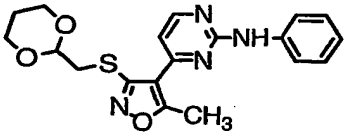
IB-2



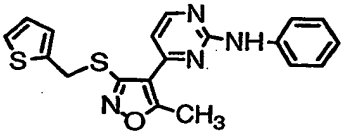
IB-3



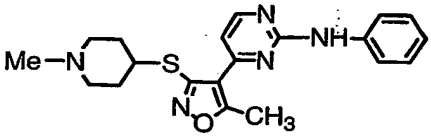
IB-4



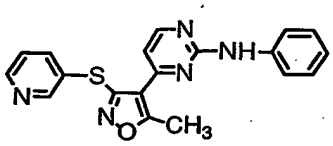
IB-4



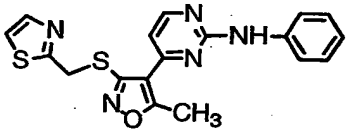
IB-5



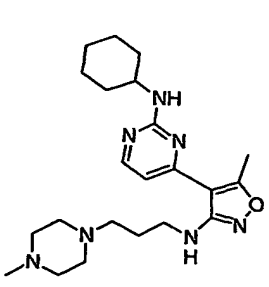
IB-6

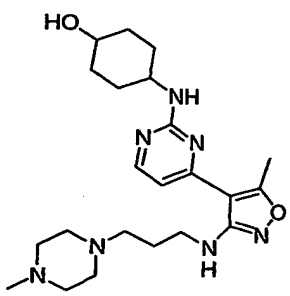


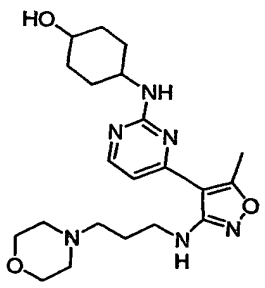
IB-7



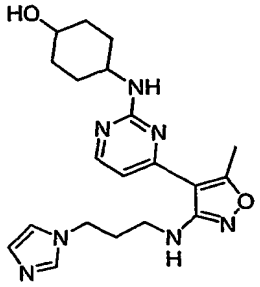
IB-8



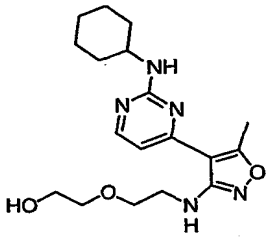




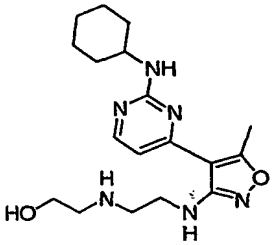
IB-9



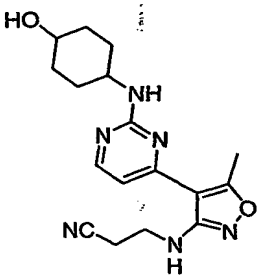
IB-10



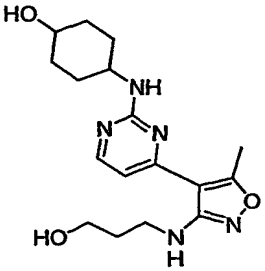
IB-11



IB-13



IB'-1



IB'-2

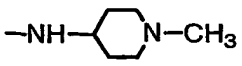
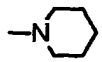
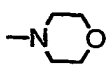
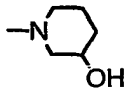
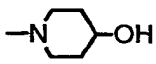
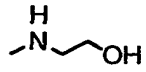
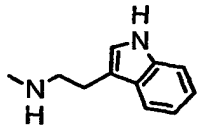
IB'-3

IB'-4

Other embodiments of this invention relate to compounds of formula **I** where G is -NH-R (formula **IC**), G is -NH-Ar (formula **ID**), G is -O-R (formula **IE**), G is -O-Ar (formula **IF**), G is $-SO_2-R$ (formula **IG**), G is $-SO_2-Ar$ (formula **IH**), G is -S(O)-R (formula **IJ**), and G is -S(O)-Ar (formula **IK**). Specific examples of these embodiments are shown below in Table 5.

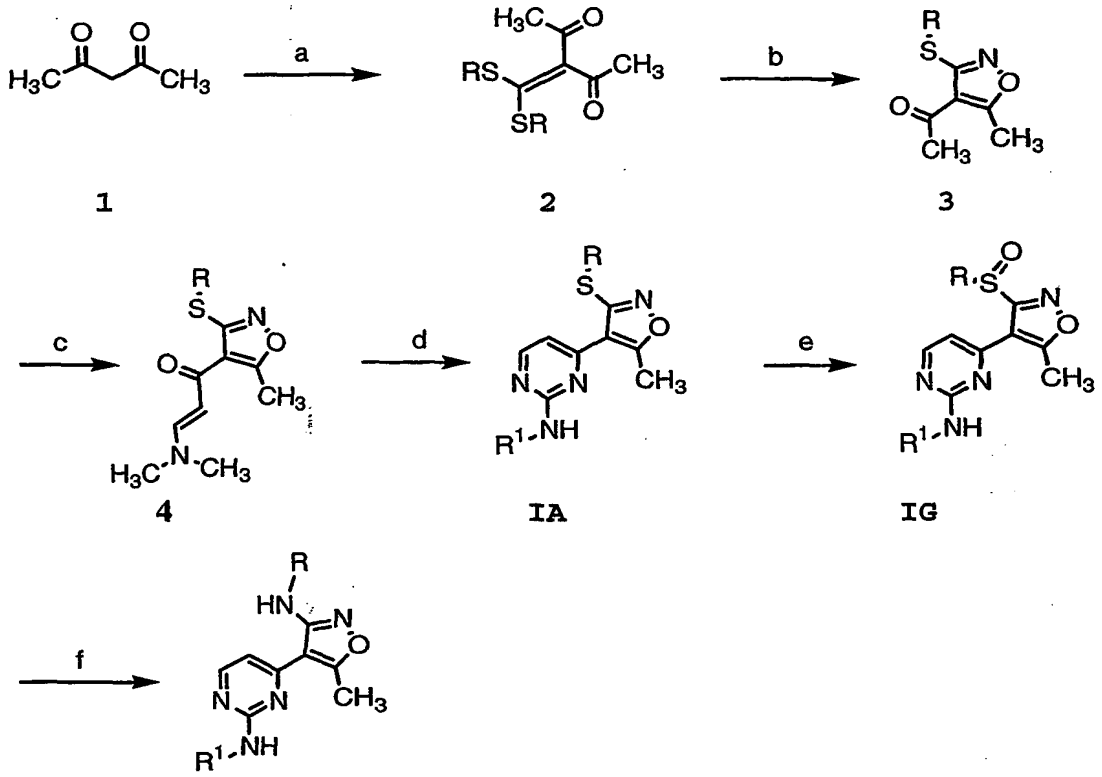
Table 5

No.	G	A	R^1	R^2
IC-1	-NH-ethyl	CH	phenyl	CH_3
IC-2	-NH-propyl	N	phenyl	CH_3
IC-3	-NH-butyl	N	3-CN-phenyl	CH_3
IC-4	-NH-isobutyl	N	phenyl	CH_3
IC-5	$-NH-CH_2CH_2N(CH_3)_2$	N	3-OCH_3-phenyl	CH_3

ID-1	-NH-phenyl	N	3-OCH_3-phenyl	CH_3
ID-2	-NH-benzyl	N	phenyl	CH_3
ID-3		N	phenyl	CH_3
ID-4		N	3,5-$(OCH_3)_2$-phenyl	CH_3
ID-5		N	3,5-$(OCH_3)_2$-phenyl	CH_3
ID-6		N	3,5-$(OCH_3)_2$-phenyl	CH_3
ID-7		N	3,5-$(OCH_3)_2$-phenyl	CH_3
ID-8		N	3,5-$(OCH_3)_2$-phenyl	CH_3
ID-9		N	phenyl	CH_3
IE-1	-O-$CH_2CH_2N(CH_3)_2$	N	4-CH_3-phenyl	CH_3
IE-2	-O-isobutyl	N	phenyl	CH_3
IF-1	-O-benzyl	N	3,4-$(OCH_3)_2$-phenyl	CH_3
IG-1	-SO_2CH_3	CH	phenyl	CH_3
IG-2	-SO_2-butyl	N	phenyl	CH_3
IH-1	-SO_2-phenyl	N	3-OCH_3-phenyl	CH_3
IH-2	SO_2-(4-CH_3-phenyl)	N	3,4-$(OCH_3)_2$-phenyl	CH_3
IH-2	SO_2-(2-naphthyl)	N	3,4-$(OCH_3)_2$-phenyl	CH_3
IJ-1	SO-butyl	N	phenyl	CH_3
IK-1	SO-phenyl	N	3-OCH_3-phenyl	CH_3

The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general scheme below and the preparative examples that follow.

Scheme I



Reagents and conditions: (a) CS_2, K_2CO_3; then, R-I; (b) H_2NOH, Et_3N, NaOEt; (c) dimethylformamide-dimethylacetal; (d) R^1-NHC(=NH)NH_2; (e) oxone; (f) R-NH_2, DMSO

Scheme I above shows a general route to prepare compounds of formulae **IA**, **IC**, **ID**, or **IG**, wherein R^2 is methyl. As shown in step (a), following the condensation of diacetone **1** with carbon disulfide, the resulting dimercaptomethylene dianion may be quenched with an iodoalkane (such as CH_3I) to give the 3-(bis-alkylsulfanyl-methylene)-pentane-2,4-dione (**2**). It will be understood by one skilled in the art that a variety of iodoalkanes may be used to provide a variety of compounds of this invention. Treatment of **2** with hydroxylamine provides the isoxazole **3**, which may then be condensed with dimethylformamide-dimethylacetal (DMF-DMA) according to step (c) to give the enamine **4**. Compound **4** may be

cyclized with various guanidine derivatives to provide compounds of formula **IA**. Oxidation of a **IA** compound with oxone provides the corresponding sulfonyl compound of formula **IG**. The sulfonyl group of **IG**, in turn, may be displaced by various amines to provide **IC** or **ID**. Alternatively, the sulfonyl group or corresponding sulfoxide group may be displaced by -SAr, -SR, -OAr, or -OR to provide other compounds of this invention.

The activity of a compound utilized in this invention as an inhibitor of JNK3, Lck, or Src, may be assayed *in vitro*, *in vivo* or in a cell line according to methods known in the art. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated JNK3, Lck, or Src. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to JNK3, Lck, or Src. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/JNK3, inhibitor/Lck, or inhibitor/Src complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with JNK3, Lck, or Src bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of JNK3, Lck, or Src kinase are set forth in the Examples below.

According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in the compositions of this invention is such that is effective to detectably inhibit a protein kinase, particularly

JNK3, Lck, or Src in a biological sample or in a patient. Preferably the composition of this invention is formulated for administration to a patient in need of such composition. Most preferably, the composition of this invention is formulated for oral administration to a patient.

The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The term "detectably inhibit", as used herein means a measurable change in JNK3, Lck, or Src activity between a sample comprising said composition and a JNK3, Lck, or Src kinase and an equivalent sample comprising

JNK3, Lck, or Src kinase in the absence of said composition.

A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$

salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their

polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic

uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition in a monotherapy, may also be present in the compositions of this invention.

For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

Other examples of agents the compounds of this invention may also be combined with include, without limitation, anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating diabetes such as insulin, insulin analogues, alpha glucosidase inhibitors,

biguanides, and insulin sensitizers; and agents for treating immunodeficiency disorders such as gamma globulin.

The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

According to another embodiment, the invention relates to a method of inhibiting JNK3, Lck, or Src kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Inhibition of JNK3, Lck, or Src kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

According to another embodiment, the invention provides a method for treating or lessening the severity of a JNK3-, Lck- or Src-mediated disease or condition in

a patient comprising the step of administering to said patient a composition according to the present invention.

The term "JNK-mediated disease", as used herein means any disease or other deleterious condition in which JNK is known to play a role. Such conditions include, without limitation, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, cancer, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase synthase-2.

Inflammatory diseases that may be treated or prevented by the compounds of this invention include, but are not limited to, acute pancreatitis, chronic pancreatitis, asthma, allergies, and adult respiratory distress syndrome.

Autoimmune diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

Destructive bone disorders that may be treated or prevented by the compounds of this invention include, but are not limited to, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma and HTLV-1 mediated tumorigenesis.

Angiogenic disorders that may be treated or prevented by the compounds of this invention include solid tumors, ocular neovasculization, infantile haemangiomas. Infectious diseases that may be treated or prevented by the compounds of this invention include, but are not limited to, sepsis, septic shock, and Shigellosis.

Viral diseases that may be treated or prevented by the compounds of this invention include, but are not limited to, acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Neurodegenerative diseases that may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, seizures, Huntington's disease, traumatic brain injury, ischemic and hemorrhaging stroke, cerebral ischemias or neurodegenerative disease, including apoptosis-driven neurodegenerative disease, caused by traumatic injury, acute hypoxia, ischemia or glutamate neurotoxicity.

"JNK-mediated diseases" also include ischemia/reperfusion in stroke, heart attacks, myocardial ischemia, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, hepatic ischemia, liver disease, congestive heart failure, pathologic immune responses such as that

caused by T cell activation and thrombin-induced platelet aggregation.

In addition, compounds of the instant invention may be capable of inhibiting the expression of inducible pro-inflammatory proteins. Therefore, other "JNK-mediated conditions" that may be treated by the compounds of this invention include edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain and arthritis pain.

The compounds of this invention are also useful as inhibitors of Src-family kinases, especially Src and Lck. The term "Src-mediated or Lck-mediated disease", as used herein means any disease or other deleterious condition in which Src or Lck is known to play a role. Accordingly, these compounds are useful for treating diseases or conditions that are known to be affected by the activity of one or more Src-family kinases. Such diseases or conditions include hypercalcemia, restenosis, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obtructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, and allergic rhinitis. Diseases that are affected by Src activity, in particular, include hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease. Diseases that are affected by Lck activity, in particular, include autoimmune diseases, allergies, rheumatoid arthritis, and leukemia.

A preferred embodiment relates to the method used to treat or prevent a JNK-mediated disease selected from inflammatory diseases, autoimmune diseases, destructive bone disorders, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, or thrombin-induced platelet aggregation.

Another preferred embodiment relates to the method used to treat or prevent a Src- or Lck-mediated disease selected from hypercalcemia, osteoperosis, osteoarthritis, or sympomatic treatment of bone metastasis.

In an alternate embodiment, the methods of this invention that utilize compositions that do not contain an additional therapeutic agent, comprise the additional step of separately administering to said patient an additional therapeutic agent. When these additional therapeutic agents are administered separately they may be administered to the patient prior to, sequentially with or following administration of the compositions of this invention.

The compounds of this invention or pharmaceutical compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition

comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

Example 1. **1-(5-Methyl-3-methylsulfanyl-isoxazol-4-yl)-ethanone (Compound 3)**: To a solution of 3-(bis-methylsulfanyl-methylene)-pentane-2,4-dione (1g, 4.89 mmol) in methylene chloride (50 ml) at room temperature was added hydroxylamine hydrochloride (0.374g, 5.38 mmol) followed by triethylamine (0.747 ml, 5.38 mmol). The reaction was stirred overnight, then partitioned between methylene chloride and water. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give 0.645g (3.77 mmol) of the title compound. ^{1}HNMR and

mass spectrum were consistent with the structure (MS m+1 = 172).

Example 2. **3-Dimethylamino-1-(5-methyl-3-methylsulfanyl-isoxazol-4-yl)-propenone (Compound 4)**: To a solution of above prepared compound 3 (0.375 g, 2.19 mmol) in toluene was added 1.5 ml of dimethylformamide-dimethylacetal. The reaction mixture was heated at 100 °C overnight resulting in complete conversion to product by thin layer chromatography (TLC). The reaction was partitioned between ethyl acetate and water. After extracting the aqueous layer with fresh ethyl acetate, the combined organic layers were concentrated and the crude product was purified by silica gel chromatograpy (2% MeOH:CH_2Cl_2) to give 0.425 g (1.88 mmol) of the title compound.

Example 3. **(3,5-Dimethoxy-phenyl)-[4-(5-methyl-3-methylsulfanyl-isoxazol-4-yl)-pyrimidin-2-yl]-amine (Compound IIA-18) and 4-[2-(3,5-dimethoxy-phenylamino)-pyrimidin-4-yl]-5-methyl-isoxazol-3-ol (Compound 5)**: To a solution of the above-prepared compound 4 (200mg, 0.884 mmol) and 3,5-dimethoxyphenyl guanidine (207mg, 1.061 mmol) in methanol was added sodium ethoxide (excess). The reaction was heated at 70 °C overnight in a sealed tube. TLC indicated complete disappearance of starting material 4 and the formation of two distinct products. The reaction was partitioned between ethyl acetate and water and the aqueous layer was extracted with fresh ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude products were purified by silica gel chromatography (2% MeOH:CH_2Cl_2) to provide 49mg (0.137 mmol) of title

compound **IIA-18** and 10 mg (0.03 mmol) of title compound 5.

Example 4. **(3,5-Dimethoxy-phenyl)-[4-(3-methanesulfinyl-5-methyl-isoxazol-4-yl)-pyrimidin-2-yl]-amine (Compound 6)**: To a solution of the above-prepared compound **IIA-18** (49 mg, 0.137 mmol) in methanol (3 ml) at room temperature was added a solution of oxone (252 mg, 0.41 mmol) in water. The reaction was stirred overnight resulting in conversion of starting material. The reaction mixture was partitioned between ethyl acetate and water, the aqueous layer was extracted with fresh ethyl acetate, and the combined organic layers were concentrated. The crude title compound (35 mg, 0.93 mmol) was used without further purification for the next step.

Example 5. **(3,5-Dimethoxy-phenyl)-[4-(5-methyl-3-piperidin-1-yl-isoxazol-4-yl)-pyrimidin-2-yl]-amine (Compound ID-4)**: To a solution of the above-prepared compound 6 (7 mg, 0.019 mmol) in ethanol (1.5 ml) was added piperidine (0.01 ml, excess). The reaction mixture was heated at 70 °C overnight resulting in conversion to product by LC/MS. The mixture was evaporated using a pierce block evaporator and purified by reverse phase preparative HPLC giving the title compound (1.7 mg, 0.004 mmol).

Four other reactions were run in parallel with the above reaction using the same procedure except that piperidine was replaced by morpholine to provide compound **ID-5**, 3-hydroxypiperidine to provide compound **ID-6**, 4-hydroxypiperidine to provide compound **ID-7**, and ethanolamine to provide compound **ID-8**. All of these

products were purified by reverse phase HPLC and characterized by both NMR and LC/MS.

Example 6. Src Inhibition Assays

The compounds were evaluated as inhibitors of human src kinase using either a radioactivity-based assay or spectrophotometric assay.

(I) Radioactivity-based assay

The compounds were assayed as inhibitors of full-length recombinant human Src kinase (from Upstate Biotechnology, cat. no. 14-117) expressed and purified from baculo viral cells. Src kinase activity was monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following were the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM $MgCl_2$, 2 mM DTT, 0.25 mg/ml BSA, 10 µM ATP (1-2 µCi ^{33}P-ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 minutes before initiating the reaction with ^{33}P-ATP. After 20 minutes of reaction, the reactions were quenched with 150 µl of 10% trichloroacetic acid (TCA) containing 20 mM Na_3PO_4. The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter plates were washed four times

with 10% TCA containing 20 mM Na_3PO_4 and then 4 times with methanol. 200µl of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount scintillation counter. The radioactivity incorporated was plotted as a function of the inhibitor concentration. The data was fitted to a competitive inhibition kinetics model to get the K_i for the compound.

(II) Spectrophotometric assay

The ADP produced from ATP by the human recommbinant src kinase-catalyzed phosphorylation of poly Glu-Tyr substrate was quanitified using a coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay one molecule of NADH is oxidized to NAD for every molecule of ADP produced in the kinase reaction. The disappearance of NADH can be conveniently followed at 340 nm.

The following were the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM $MgCl_2$, 2 mM DTT, 0.25 mg/ml poly Glu-Tyr, and 25 nM of recombinant human Src kinase. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 200 µM NADH, 30 µg/ml pyruvate kinase and 10 µg/ml lactate dehydrogenase.

In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 minutes before initiating the reaction with 100 µM ATP. The absorbance change at 340 nm with time,

the rate of the reaction, was monitored on a molecular devices plate reader. The data of rate as a function of the inhibitor concentration was fitted to competitive inhibition kinetics model to get the K_i for the compound.

Many of the present compounds tested in the Src inhibition assays provided an IC_{50} value below one micromolar.

Example 7. Lck Inhibition Assays

The compounds were evaluated as inhibitors of human src kinase using either a radioactivity-based assay or spectrophotometric assay.

(I) Radioactivity-based assay

The compounds were assayed as inhibitors of full-length bovine thymus Lck kinase (from Upstate Biotechnology, cat. no. 14-106) expressed and purified from baculo viral cells. Kinase activity was monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following were the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM $MgCl_2$, 2 mM DTT, 0.25 mg/ml BSA, 10 µM ATP (1-2 µCi ^{33}P-ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 minutes before initiating the reaction with ^{33}P-ATP. After 20 minutes of reaction, the reactions were quenched with 150 µl of 10% trichloroacetic acid (TCA)

containing 20 mM Na_3PO_4. The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter plates were washed four times with 10% TCA containing 20 mM Na_3PO_4 and then 4 times with methanol. 200µl of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount scintillation counter. The radioactivity incorporated was plotted as a function of the inhibitor concentration. The data was fitted to a competitive inhibition kinetics model to get the Ki for the compound.

(II) Spectrophotometric assay

The ADP produced from ATP by the human recombinant Lck kinase-catalyzed phosphorylation of poly Glu-Tyr substrate was quanitified using a coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay one molecule of NADH is oxidised to NAD for every molecule of ADP produced in the kinase reaction. The disappearance of NADH can be conveniently followed at 340 nm.

The following were the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM $MgCl_2$, 2 mM DTT, 5 mg/ml poly Glu-Tyr, and 50 nM of recombinant human Lck kinase. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 200 µM NADH, 30 µg/ml pyruvate kinase and 10 µg/ml lactate dehydrogenase.

In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO were added to the wells to give a final DMSO

concentration of 2.5%. The assay plate was incubated at 30 °C for 10 minutes before initiating the reaction with 150 μM ATP. The absorbance change at 340 nm with time, the rate of the reaction, was monitored on a molecular devices plate reader. The data of rate as a function of the inhibitor concentration was fitted to competitive inhibition kinetics model to get the K_i for the compound.Many of the present compounds tested in the Lck inhibition assays provided an IC_{50} value below one micromolar.

Example 8. Cloning, Expression and Purification of JNK3 Protein

A BLAST search of the EST database using the published JNK3α1 cDNA as a query identified an EST clone (#632588) that contained the entire coding sequence for human JNK3α1. Polymerase chain reactions (PCR) using *pfu* polymerase (Strategene) are used to introduce restriction sites into the cDNA for cloning into the pET-15B expression vector at the NcoI and BamHI sites. The protein is expressed in *E. coli*. Due to the poor solubility of the expressed full-length protein (Met 1-Gln 422), an N-terminally truncated protein starting at Ser residue at position 40 (Ser 40) is produced. This truncation corresponds to Ser 2 of JNK1 and JNK2 proteins, and is preceded by a methionine (initiation) and a glycine residue. The glycine residue is added in order to introduce an NcoI site for cloning into the expression vector. In addition, systematic C-terminal truncations are performed by PCR to identify a construct that give rise to diffraction-quality crystals. One such

construct encodes amino acid residues Ser40-Glu402 of JNK3α1 and is preceded by Met and Gly residues.

The construct is prepared by PCR using deoxyoligonucleotides:

5' GCTCTAGAGCTCCATGGGCAGCAAAAGCAAAGTTGACAA 3' (forward primer with initiation codon underlined)(SEQ ID NO:1) and 5' TAGCGGATCCTCATTCTGAATTCATTACTTCCTTGTA 3' (reverse primer with stop codon underlined)(SEQ ID NO:2) as primers and is confirmed by DNA sequencing. Control experiments indicated that the truncated JNK3 protein had an equivalent kinase activity towards myelin basic protein when activated with an upstream kinase MKK7 *in vitro*.

E. coli strain BL21 (DE3) (Novagen) is transformed with the JNK3 expression construct and grown at 30°C in LB supplemented with 100 µg/ml carbenicillin in shaker flasks until the cells were in log phase (OD_{600} ~ 0.8). Isopropylthio-β-D-galactosidase (IPTG) is added to a final concentration of 0.8 mM and the cells are harvested 2 hours later by centrifugation.

E. coli cell paste containing JNK3 is resuspended in 10 volumes/g lysis buffer (50 mM HEPES, pH 7.2, containing 10% glycerol (v/v), 100 mM NaCl, 2 mM DTT, 0.1 mM PMSF, 2 µg/ml Pepstatin, 1µg/ml each of E-64 and Leupeptin). Cells are lysed on ice using a microfluidizer and centrifuged at 100,000 x *g* for 30 minutes at 4 °C. The 100,000 x *g* supernatant is diluted 1:5 with Buffer A (20 mM HEPES, pH 7.0, 10% glycerol (v/v), 2 mM DTT) and purified by SP-Sepharose (Pharmacia) cation-exchange chromatography (column dimensions: 2.6 x 20 cm) at 4 °C. The resin is washed with 5 column volumes of Buffer A, followed by 5 column volumes of Buffer A containing 50 mM NaCl. Bound JNK3 is eluted with a 7.5

column volume linear gradient of 50-300 mM NaCl. JNK3 eluted between 150-200 mM NaCl.

Example 9. Activation of JNK3

5 mg of JNK3 is diluted to 0.5 mg/ml in 50 mM HEPES buffer, pH 7.5, containing 100 mM NaCl, 5 mM DTT, 20 mM $MgCl_2$ and 1 mM ATP. GST-MKK7(DD) is added at a molar ratio of 1:2.5 GST-MKK7:JNK3. After incubation for 30 minutes at 25°C, the reaction mixture is concentrated 5-fold by ultrafiltration in a Centriprep-30 (Amicon, Beverly, MA), diluted to 10 ml and an additional 1 mM ATP added. This procedure is repeated three times to remove ADP and replenish ATP. The final addition of ATP is 5 mM and the mixture incubated overnight at 4°C.

The activated JNK3/GST-MKK7(DD) reaction mixture is exchanged into 50 mM HEPES buffer, pH 7.5, containing 5 mM DTT and 5% glycerol (w/v) by dialysis or ultrafiltration. The reaction mixture is adjusted to 1.1 M potassium phosphate, pH 7.5, and purified by hydrophobic interaction chromatography (at 25 °C) using a Rainin Hydropore column. GST-MKK7 and unactivated JNK3 do not bind under these conditions such that when a 1.1 to 0.05 M potassium phosphate gradient is developed over 60 minutes at a flow rate of 1 ml/minute, doubly phosphorylated JNK3 is separated from singly phosphorylated JNK. Activated JNK3 (i.e. doubly phosphorylated JNK3) is stored at -70°C at 0.25-1 mg/ml.

Example 10. JNK Inhibition Assay

Compounds are assayed for the inhibition of JNK3 by a spectrophotometric coupled-enzyme assay. In this assay, a fixed concentration of activated JNK3 (10 nM) is incubated with various concentrations of a

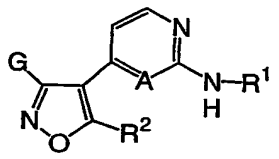
potential inhibitor dissolved in DMSO for 10 minutes at 30°C in a buffer containing 0.1 M HEPES buffer, pH 7.5, containing 10 mM $MgCl_2$, 2.5 mM phosphoenolpyruvate, 200 µM NADH, 150 µg/mL pyruvate kinase, 50 µg/mL lactate dehydrogenase, and 200 µM EGF receptor peptide. The EGF receptor peptide has the sequence KRELVEPLTPSGEAPNQALLR(SEQ ID NO:3), and is a phosphoryl acceptor in the JNK3-catalyzed kinase reaction. The reaction is initiated by the addition of 10 µM ATP and the assay plate is inserted into the spectrophotometer's assay plate compartment that is maintained at 30°C. The decrease of absorbance at 340 nm is monitored as a function of time. The rate data as a function of inhibitor concentration is fitted to competitive inhibition kinetic model to determine the K_i.

While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound having the formula:



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or a pharmaceutically acceptable derivative thereof, wherein:

G is -XR or -XAr;

each X is independently selected from a C_{1-6} alkylidene chain wherein one or two non-adjacent methylene units of X are optionally and indpendently replaced by -O-, -NR-, -S-, -C(O)-, -C(O)NR-, -NRC(O)-, -NRC(O)NR-, -SO-, $-SO_2-$, $-NRSO_2-$, $-SO_2NR-$, or $-NRSO_2NR-$;

A is N or CR;

each R is independently selected from hydrogen or an optionally substituted C_{1-8} aliphatic group, or two R groups bound to the same nitrogen are taken together with the nitrogen to form a 3-7 membered heterocyclic ring having 0-2 heteroatoms in addition to the nitrogen, and independently selected from nitrogen, oxygen, or sulfur; provided that when G is $-N(R)_2$, the two R groups are not taken together to form a ring;

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or aryl monocyclic ring having zero to three heteroatoms independently selected from nitrogen, sulfur, or oxygen, or an optionally substituted 8-10 membered saturated, partially unsaturated, or aryl bicyclic ring having zero to four

heteroatoms independently selected from nitrogen, sulfur, or oxygen;

R^1 is $T_{(n)}$-R or $T_{(n)}$-Ar;

n is zero or one;

T is selected from -C(O)-, $-CO_2-$, -C(O)C(O)-, $-C(O)CH_2C(O)-$, -CONR-, $-S(O)_2-$, or $-S(O)_2NR-$; and

each R^2 is independently selected from -R, $-CH_2OR$, -CH(O), $-CH_2SR$, $-CH_2S(O)_2R$, $-CH_2C(O)R$, $-CH_2CO_2R$, $-CH_2CN$, $-CH_2N(R)_2$, -CH=N-OR, $-CH=NN(R)_2$, -CH=NNHCOR, $-CH=NNHCO_2R$, $-CH=NNHSO_2R$, Ar, $-CH_2Ar$, $-CH_2NRCON(R)_2$, $-CH_2NRCOR$, $-CH_2NRCO_2R$, $-CH_2CON(R)_2$, $-CH_2SO_2N(R)_2$, or $-CH_2NRSO_2N(R)_2$.

2. The compound according to claim 1, wherein:

G is -X-R or -X-Ar, wherein:

each X is independently selected from a C_{1-4} alkylidene chain, wherein one or two non-adjacent methylene units of X are independently replaced by -S-, -SO-, $-SO_2-$, -O-, or -NH-;

R is an optionally substituted C_{1-6} aliphatic group; and

Ar is an optionally substituted 5-6 membered saturated or aryl ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered bicyclic aryl or heteroaryl ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

3. The compound according to claim 2, wherein:

R is a C_{1-4} aliphatic group optionally substituted with halo, CN, oxo, $N(R^\circ)_2$, OH, OR°, CO_2R°, $C(O)R^\circ$, $C(O)N(R^\circ)_2$, $NR^\circ CO_2R^\circ$, SR°, $NR^\circ SO_2R^\circ$, SO_2R°, $NR^\circ C(O)R^\circ$, $OC(O)R^\circ$, or $NR^\circ C(O)N(R^\circ)_2$, wherein each R° group is

independently selected from hydrogen or C_{1-4} aliphatic; and

Ar is an optionally substituted ring selected from phenyl, pyridyl, imidazolyl, thienyl, thiazolyl, [1,3]dioxanyl, piperidinyl, morpholinyl, pyrrolyl, pyrrolidinyl, furanyl, tetrahydrofuranyl, pyranyl, imidazolyl, benzimidazolyl, pyrrolyl, piperazinyl, thiomorpholinyl, naphthyl, oxazolyl, triazinyl, tetrazolyl, dithiolanyl, dioxalanyl, benzofuranyl, benzothienyl, or indolyl.

4. The compound according to claim 2, wherein:

R^2 is selected from R, $CH_2N(R)_2$, or CH_2Ar, wherein:

each R is independently selected from hydrogen or optionally substituted C_{1-4} aliphatic, and

Ar is an optionally substituted 6 membered saturated or unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

5. The compound according to claim 1, wherein:

R^1 is $T_{(n)}$-Ar, wherein n is zero; and

Ar is selected from an optionally substituted 6-membered saturated or aryl ring having 0-2 nitrogens, or an optionally substituted 9-10 membered partially unsaturated or fully unsaturated bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

6. The compound according to claim 5, wherein:

R^1 is phenyl, cyclohexyl, pyridyl, naphthyl, quinolinyl, isoquinolinyl, or indanyl, wherein:

R^1 is optionally substituted with 1-3 groups independently selected from R°, halogen, NO_2, CN, OR°, SR°, $N(R^\circ)_2$, CO_2R°, $C(O)R^\circ$, $CON(R^\circ)_2$, phenyl, SO_2R°, or $NR^\circ C(O)R^\circ$, wherein each R° is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic.

7. The compound according to claim 6, wherein R^1 is optionally substituted with 1-3 groups independently selected from methyl, ethyl, oxo, CF_3, OMe, C(O)Me, C(O)phenyl, CH≡CH, CO_2H, $C(O)NH_2$, SMe, CO_2Me, fluoro, SO_2Me, NO_2, CN, chloro, $N(Me)_2$, NHC(O)Me, NH_2, cyanophenyl, CO_2Et, CH_2OH, CH_2OMe, 3-CH_2CO_2H-phenyl, or 3-$CH_2CH_2CO_2H$-phenyl.

8. The compound according to claim 5, wherein:
R^2 is selected from R, $CH_2N(R)_2$, or CH_2Ar, wherein:
each R is independently selected from hydrogen or optionally substituted C_{1-4} aliphatic, and
Ar is an optionally substituted 6 membered saturated or unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

9. A compound selected from the group consisting of the following compound numbers:
IIA-1, IIA-2, IIA-3, IIA-4, IIA-5, IIA-6,
IIA-7, IIA-8, IIA-9, IIA-10, IIA-11, IIA-12,
IIA-13, IIA-14, IIA-15, IIA-16, IIA-17, IIA-18,
IIA-19, IIA-20, IIA-21, IIA-22, IIA-23, IIA-24,
IIA-25, IIA-26, IIA-27, IIA-28, IIA-29, IIA-30,
IIA-31, IIA-32, IIA-33, IIA-34, IIA-35, IIA-36,
IIA-37, IIA-38, IIA-39, IIA-40, IIA-41, IIA-42,

IIA-43, IIA-44, IIA-45, IIA-46, IIA-47, IIA-48, IIA-49, IIA-50, IIA-51, IIA-52, IIA-53, IIA-54, IIA-55, IIA-56, IIA-57, IIA-58, IIA-59, IIA-60, IIA-61, IIA-62, IIA-63, IIA-64, IIA-65, IIA-66, IIA-67, IIA-68, IIA-69, IIA-70, IIA-71, IIA-72, IIA-73, IIA-74, IIA-75, IIA-76, IIA-77, IIA-78, IIA-79, IIA-80, IIA-81, IIA-82, IIA-83, IIA-84, IIA-85, IIA-86, IIA-87, IIA-88, IIA-89, IIA-90, IIA-91, IIA-92, IIA-93, IIA-94, IIA-95, IIA-96, IIA-97, IIA-98, IIA-99, IIA-100, IIA-101, IIA-102, IIA-103, IIA-105, IIA-106, IIA-107, IIA-108, IIA-109, IIA-110, IIA-111, IIA-112, IIA-113, IIA-114, IIA-115, IIA-116, IIA-117, IIA-118, IIA-119, IIA-120, IIA-121, IIA-122, IIA-123, IIA-124, IIA-125, IIA-126, IIA-127, IIA-128, IIA-129, IIA-130, IIA-131, IIA-132, IIA-133, IIA-134, IIA-135, IIA-136, IIA-137, IIA-138, IIA-139, IIA-140, IIA-141, IIA-142, IIA-143, IIA-144, IIA-145, IIA-146, IIA-147, IB-1, IB-2, IB-3, IB-4, IB-4, IB-5, IB-6, IB-7, IB-8, IB-9, IB-10, IB-11, IB-13, IB'-1, IB'-2, IB'-3, IB'-4, IC-1, IC-2, IC-3, IC-4, IC-5, ID-1, ID-2, ID-3, ID-4, ID-5, ID-6, ID-7, ID-8, ID-9, IE-1, IE-2, IF-1, IG-1, IG-2, IH-1, IH-2, IH-2, IJ-1, and IK-1.

10. A composition comprising a compound according to any of claims 1-9 in an amount to detectably inhibit JNK3, Lck, or Src kinase activity, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

11. The composition according to claim 10, additionally comprising an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a

neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

12. A method of inhibiting JNK3, Lck, or Src kinase activity in a biological sample comprising the step of contacting said biological sample with:

a) a compound according to claim 1; or

b) a composition according to claim 10.

13. A method of treating or lessening the severity of a JNK3-, Lck-, or Src-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to claim 10.

14. A method of treating or lessening the severity of an inflammatory disease, autoimmune disease, destructive bone disorder, proliferative disorder, infectious disease, neurodegenerative disease, allergy, reperfusion/ischemia in stroke, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or a condition associated with proinflammatory cytokines comprising the step of administering to said patient a composition according to claim 10.

15. The method according to claim 14, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

16. The method according to claim 14, wherein said method is used to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

17. The method according to claim 14, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

18. The method according to claim 14, wherein said method is used to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

19. The method according to claim 14, wherein said method is used to treat or prevent neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

20. The method according to claim 14, wherein said method is used to treat or prevent ischemia/reperfusion

in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

21. The method according to claim 14, wherein said method is used to treat or prevent a condition associated with T-cell activation or pathologic immune responses.

22. The method according to claim 14, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.

23. The method according to claim 13, wherein said disease is selected from hypercalcemia, restenosis, hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obtructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, or allergic rhinitis.

24. The method according to claim 23, wherein said disease is selected from hypercalcemia, osteoperosis, osteoarthritis, or sympomatic treatment of bone metastasis.

25. The method according to claim 13, wherein said disease is selected from autoimmune diseases, allergies, rheumatoid arthritis, and leukemia.

26. The method according to claim 13, comprising the additional step of administering to said patient an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

27. A composition for coating an implantable device comprising a compound according to claim 1 and a carrier suitable for coating said implantable device.

28. An implantable device coated with a composition according to claim 27.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 02/11609

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 A61K31/505 C07D413/04 C07D417/14 A61K31/4439
A61P37/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 12621 A (VERTEX PHARMACEUTICALS INCORPORATED, USA) 22 February 2001 (2001-02-22) see compounds IIA-23, IIA86,IIA90 claims; table 1	1-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2002	30/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, J-C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

mational application No.
PCT/US 02/11609

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/11609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0112621 1 A		NONE	